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The Blood-Brain Connection of Alzheimer's Disease: Another Glance after Quarter of a Century

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative cognitive disorder. In recent years, the distinction between AD and vascular dementia has become less clear, as cardiovascular morbidity is commonly exhibited in the AD brain. Nitric oxide (NO) plays multiple roles in the brain and its relationship with AD pathogenesis has previously been explored. Aberrant functioning of the neurovascular unit (NVU) is now known to jeopardize blood-brain barrier integrity, and such abnoramality seems to appear early in AD. Studies on molecular aspects of NVU dysfunction and recent advances on neuroimaging could lead to the possibility of earlier detection of preclinical AD. This review briefly surveys the progress on deciphering the intimate neuro-cardiovascular connections associated with AD and relevant advances towards the developments of translational, neuroimaging, and electrophysiological biomarkers. The current evidence suggests accurate early diagnosis of preclinical AD could be made possible by combination uses of these markers, thereby allowing earlier meaningful therapeutic intervention.

Keywords: *Alzheimer's disease; Nitric oxide; Neurovascular unit; Biomarkers; Early detection*

Background

It has been over two decades since we examined the role of nitric oxide (NO) in the pathogenesis of Alzheimer's disease (AD). NO is a potent vasodilator, a neuro-messenger associated with memory consolidation, and plays immunological roles. It was concluded that NO and its synthesizing enzymes have intricate relationships with AD [1]. Clinically, the demarcation between AD and vascular dementia has become increasingly blurry [2]. Cardiovascular and metabolic disorders appear to intimately associated with the development of cognitive impairments [3, 4]. At the cellular level, endothelial cell dysfunction is evident in hypertension, hypercholesterolemia, and diabetes, thereby leading to aberrant vascular regulation [5, 6]. Similar to the periphery, endothelial linings of brain vessels are also compromised. As neurons, neuroglia, and the endothelium form a functional unit, researchers have proposed that neurovascular dysfunction could be an important upstream culprit for dementing disorders [7]. The hypothesis has since been studied from various perspectives [8-10]. This paper aims to take a glimpse at the most recent advances on related topics.

Neurovascular dysfunction and Alzheimer's disease

It has been well-recognized that the neurovascular unit (NVU) – comprising of neurons, neuroglia, and the endothelium – maintain the integrity of the blood-brain barrier (BBB) and regulate cerebral blood flow. Previous studies have demonstrated that NVU dysfunction contributes significantly to neurodegeneration [11]. We also hypothesized that such pathology could be an early culprit for neurodegenerative dementias [12]. Animal studies have shown that amyloid or tau pathology would cause brain vessel abnormalities and BBB breakdown [13]. These pathologies have since been shown to develop early during the disease process [14].

NO is produced by four types of nitric oxide synthases (NOS). In the brain, neurons, glial cells, and the endothelium are responsible for its synthesis. Classically, the endothelial form of NOS has been consistently associated with neuroprotection [15]. The inducible NOS - due to its high magnitude of NO release – leads to neurotoxicity as a result of oxidative stress [16]. Neuronal NOS appears to be yielding variable findings [17, 18]. In more recent animal studies, the molecular signaling effects of NO on AD pathogenesis are being elucidated. NO appears to downregulate an essential transporter in myelin-

forming oligodendrocytes, which could be contributing to AD onset [19]. NOS isoenzymes appear to possess multiple roles in the dysfunctional NVU. In a mouse model expressing mutated tau, neurovascular uncoupling secondary to the dissociation of neuronal NOS from postsynaptic densities has been observed. This phenomenon leads to reduce NO production and vasodilation during glutamatergic synapse activities [20]. Research on endothelial NOS-knockout mice showed the endothelial NOS-derived NO appears to be neuroprotective during the aging process, possibly by modulating amyloid precursor protein processing in cerebrovascular endothelium and neuronal tissue [21]. The inducible form of NOS has consistently been associated with neurotoxic effects as it is upregulated during inflammatory response, causing nitrosative stress [22, 23]. From these studies, constitutionally-produced NO by the neuronal and endothelial NOS isoforms appear to be disturbed during neurovascular decoupling – the prelude to NVU dysfunction [20, 24].

Both the astrocytes and pericytes are essential components of the NVU. We previously proposed that astrocytes being an important player in amyloid production through the interaction between S100β peptide and receptor for advanced glycation end product (RAGE) in the ischemic brain [12]. In a recent transgenic animal model of AD, a unique group of astrocytes have been identified – the "disease-associated astrocytes". These cells are found to be in close proximity to the amyloid oligomers and they appear early in the mouse brain prior to any observed cognitive decline [25]. Interestingly, similar cells are also found in the post-mortem brains of AD patients [26]. Pericyte abnormalities have also been noted in animal AD models and in human [27]. AD patients who are apolipoprotein E4 carriers appear to have accelerated pericytic damages [28]. Furthermore, pericyte loss, being assessed by its marker platelet-derived growth factor receptor-β (PDGFR-β), contributes significantly to BBB breakdown [28]. Retinal PDGFR-β decrease has been shown to be correlated to amyloid burden and severity of cognitive decline – from mild cognitive impairments to severe AD - in a human study [27]. In another recent human study, apolipoprotein E4 allele has been shown to be associated with increased hippocampal and medial temporal BBB breakdown, independent of amyloid or tau pathology. Moreover, such abnormality appears even in asymptomatic subjects and is more severe when cognitive deficits become apparent [29]. Taken together, NVU dysfunction and subsequent BBB breakdown appear to begin early during the neurodegenerating process [9, 14].

Alzheimer's disease – one step closer to earlier detection?

The large-scale Scandinavian study to examine vascular risk factors and cognitive performance in the elderly population published five years ago reminded us again cardiovascular risk factors are significantly correlated to AD development [30]. AD has been coined "type III diabetes" for more than a decade ago [31]. Primary and secondary preventions have been the advocated management strategies for cardiovascular diseases. For patients with milder cognitive impairments and AD, evidence also clearly suggests the benefits of early intervention [32]. A number of cerebrospinal fluid and blood biomarkers have been developed during the past decade, including those that represent AD hallmarks [33]. These markers, however, only indicate the presence and severity of disease, and their detections bear little relevance on altering the course of the illness. In order to optimize treatment outcome, early detection is therefore warranted. With the sufficient evidence that NVU derangement occurs relatively early in AD, the possibility of developing reliable early biomarkers could become a foreseeable option [34, 35].

In addition to its RAGE binding and subsequent β-site amyloid precursor protein cleaving enzyme upregulation, increases in S100β and neuron-specific enolase levels during BBB opening have been demonstrated [36]. Such findings implicate the feasibility of using these as early serum markers for NVU dysfunction and BBB breach [8, 14, 37]. Glial fibrillary acidic protein (GFAP) is an intermediate filament protein prominently expressed in astrocytes, playing a critical role in astrocytic-neuronal communication [38]. GFAP is not usually present in the periphery; its expression increased significantly during astrogliosis and has been used as a non-specific marker for brain injuries [39]. In a recent study, GFAP has been shown to be elevated in the plasma of AD subject [40]. Ubiquitin carboxyl-terminal esterase L1 is a neuron-specific cytoplasmic enzyme that could be another candidate to measure BBB breakdown [41, 42].

Advances in neuroimaging have allowed remarkable structural and functional visualizations of the ailing brain. Amyloid- and tau-imaging have been used to identify these AD markers [43, 44]. Although these peptides could be observed in preclinical stages of AD, they alone show variable accuracies in relation to the presence of disease [45, 46]. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been accepted as a non-invasive imaging modality to examine BBB integrity. It utilizes a gadolinium-based contrast with molecules small enough to cross a disrupted BBB [47]. Arterial spin labelling MRI is another in vivo tomographic technology that has been developed to quantitatively assess cerebral blood flow [36]. On functional imaging, resting state functional MRI (rs-fMRI) has been deployed to measure blood oxygenation level-dependent (BOLD) signal fluctuation in brain regions of psychiatric and medical patients [48]. Several studies have suggested that alterations in BOLD signaling measured in rs-MRI are implicated in early AD [49]. Functional near-infrared

spectroscopy (fNIRS) is a tool to measure neuronal activities - by detecting hemoglobin concentration changes - that has found its way into evaluating childhood psychiatric presentations [50, 51]. It has been proposed that fNIRS, in combination with other technologies such as dynamic retinal vessel analysis, could offer promising outcomes in predicting vascular cognitive impairments [52, 53].

Electroencephalography (EEG) has been a well-established method to measure brain electrical activities. It has been deemed accurate in differentiating non-demented and demented patients, and could be useful in determining various disease stages [33, 54]. EEG has been used in combination with fNIRS to measure cerebral hemodynamic changes in human performing cognitive tasks [55-57]. In a recent study, EEG data discovered a non-linear relationship with amyloid burden, indicating neuronal compensatory activities during the early preclinical phase of AD [58].

Concluding remarks

Since our previous studies twenty-five years ago in examining the complex relationship between NO and AD, vascular disturbance has been increasingly recognised as an important aetiology in AD pathogenesis, with neurovascular dysfunction being an early pathology. We proposed that astrocyte would likely be an influential "co-star in the dementia drama", research has demonstrated that the non-neuronal components of the NVU, not limiting to astrocytes, show aberrant functioning during the dementing process, from neurovascular uncoupling to BBB breakdown.

Since the discovery of AD in 1906, there has been no disease-changing therapeutic breakthrough despite decades of furious research. One possible reason for such failure is "too little too late". The notions of finding one "magical bullet" to halt the disease progress (too little) and to successfully treat the illness when patients are already exhibiting prominent cognitive and non-cognitive symptoms (too late) are unrealistic. Much earlier detection and interventions are therefore highly warranted.

Recent advances in neuroscientific research and neuroimaging techniques should make early detection, or even prediction, of preclinical AD possible. The combination uses of peripheral blood markers of brain microcirculation lesions and multiple structural, functional, and electrophysiological measures discussed here would constitute an informative panel to aid timely diagnosis. Further studies to assess efficacies of early or preventive interventions, using the obtained panel diagnostic results, could possibly revolutionize AD management strategies.

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